REMARKS

Double Patenting Rejection of Claims 1, 2 and 5-10

Claims 1, 2 and 5-10 continue to be rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-36 of co-pending Application No. 08/549,792 (now U.S. 6,469,012), in view of Courtois et al., Tay et al., Beretta et al. and Chancellor et al. In an effort to expedite prosecution, Applicants submit herewith a terminal disclaimer, as requested by the Examiner. The Double Patenting rejection is now rendered moot.

35 U.S.C.§ 103(a) Rejection of Claims 1, 2 and 5-10

The claims continue to be further rejected under 35 USC 103(a) as being unpatentable over WO 94/28902 (U.S. 6.469,012), in view of Courtois et al., Tay et al., Beretta et al. and Chancellor et al. In particular, the Examiner notes that WO94/28902 teaches the oral administration of vasoactive compounds useful in the treatment of MED. Specifically, the Examiner points out that sildenafil selectively inhibits PDE5 enzyme, leading to an elevation of cGMP levels in corpus cavernorsum tissue, causing tissue relaxation and penile erection. The Examiner acknowledges that the reference does not disclose that the above-described method is useful for the treatment of a man with a spinal cord injury.

The Examiner contends that Courtois et al. teaches two pathways of erectile functions: (1) sacral, responsible for reflexogenic erection; and (2) throracic-lumbar, responsible for psychogenic erection. The Examiner concludes that spinal cord injury does not block all the pathways, citing pages 629-631.

The Examiner contends that Tay et al. teaches that ED, caused by injured spinal cord, may be psychogenic, not organic. The Examiner also contends that Berreta et al. and Chancellor et al. teach vasoactive compounds, useful in the treatment of ED for men with spinal cord injuries.

According to the Examiner, therefore, it would have been *prima facie* obvious to a person of ordinary skill in the art to employ the vasoactive

compounds, described by Applicants, for the treatment of ED in men with spinal cord injury, including those exhibiting essentially no residual erectile function. In arriving at this conclusion, the Examiner makes the following points:

(1) One of ordinary skill in the art would be motivated to use Applicants' vasoactive compounds for the treatment of ED in men with spinal cord injury, having essentially no residual erectile function, because the general established mechanism of sildenafil indicates it will be useful for treatment of ED in men with proper corpus cavernorsum tissue, including those with injured spinal cord;

(2) One of ordinary skill in the art would have a reasonable expectation that sildenafil would be useful for treatment of ED in men, including those with essentially no residual erectile function, because not all spinal cord injuries cause ED and not all ED caused by spinal cord injury are organic;

(3) One of ordinary skill in the art would be motivated to employ vasocative compounds for the treatment of ED in men with spinal cord injury, because vasoactive compounds were known as useful for treating ED in men with spinal cord injury; and

(4) An agent known to be useful for treating ED in men with spinal cord injury would reasonably be expected to be useful for treating ED caused by spinal cord injury in any man, including one exhibiting no residual erectile function.

Applicants traverse the rejection of Claims 1, 2 and 5-10 and respectfully request that the Examiner reconsider the rejection of the claims. Applicants maintain that the Examiner has not established a *prima facie* case of obviousness. To establish a prima facie case of obviousness, three basic criteria must be met: (1) There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) There must be a reasonable expectation of success; and (3) The prior art reference (or references when combined) must teach or suggest all the claim limitations.

Applicants submit there is no motivation to combine or modify US

6,469,012 (hereinafter "Ellis") and the above-mentioned secondary references to arrive at Applicants invention. In particular, Ellis provides for a method of treating ED in a male animal, comprising administering an effective amount of the compound of formula (I), described therein. Ellis et al further notes that the majority of males suffering from ED stems from organic, rather than psychogenic origin. (US 6,469,012; Col. 1, lines 18-21). As conceded by the Examiner, Ellis does not teach a method of treating ED in men with spinal cord injury. Likewise, Ellis does not teach a method of treating ED in men with spinal cord injury, having essentially no residual erectile function. Furthermore, one of ordinary skill in the art would have no expectation of success or motivation from Ellis that Applicants' compounds would be useful for treating ED in men having spinal cord injury, especially with those having little or no residual erectile function.

Courtois et al teaches that "[t]he residual erectile capacity of spinal cord injured patients is a function of the remaining neural connections within the genital system. (Courtois, pg 629 Col.1). Courtois further states that the vast majority of spinal cord injured subjects maintain a residual erectile capacity. Id. at Col. 2. According to Courtois, therefore, effectiveness of pharmacological treatments can be enhanced by the residual erectile capacity of the individual. Id. at Col. 1. Furthermore,

> Sexual rehabilitation of spinal cord injured subjects should emphasize the individual's residual capacity as a function of remaining functional pathways and should maximize this early post-traumatic potential. According to this view, lesions located above the dual innervation of the genital system (AP) or between the two pathways (BTW) should be trained to use a reflexogenic mode of sexual function, while those with lesions to the conus terminalis (CT) or cauda equina (CE) should be trained to use a pychogenic mode of function.

The absence of both pyschogenic and reflexogenic erections in a patient whose clinical evaluation reveals extended damage to both pathways is consistent with organic aetiology. Pg. 631 (Col. 2). Accordingly, Courtois does not disclose, as stated by the Examiner, that spinal cord injury "does not block all the pathways." Furthermore, Courtois does not disclose treatment for those patients having essentially no residual erectile function, but focuses on sexual rehabiliation based upon residual sexual capacity. With respect to those

treatments discussed in Courtois, none of the methods employed oral administration of a therapeutic compound for the treatment of ED.

Beretta et al teaches that transdermal application of Minoxidil to treat ED in men suffering from spinal cord injury was effective for 26.6% of the patients studied. (pg. 29; Col. 1). The study was limited to those patients who were able to obtain an erection sufficient for vaginal penetration after Prostaglandin E1 injection. Accordingly, the treatment of ED in those patients by administering Minoxidil was only about 25% successful. Beretta also discloses the disadvantages of utilizing intracavernous injections for the treatment of ED, citing, *inter alia,* the side effects of priapism and prolonged erection. Beretta does not disclose oral adminstration of a therapeutic compound for treatment of ED.

In contrast to Beretta, Chancellor et al disclosed that topical application of Minoxidil caused minimal, if any, response subjectively and objectively, after topical administration to men, having spinal cord injuries. (pg. 366, col. 2). In particular, Chancellor reports that on the patients' subjective rating scale of zero to ten, the mode was zero for Minoxidil. Id. at 367, Col. 2. Chancellor teaches other methods of treating ED in men having spinal cord injury, including vacuum constriction devices and intracorporeal injections of, *inter alia,* papaverine. Chancellor also teaches that oral administration of alpha-adrenergic antagonists, such a yohimbine, has also had "limited" success, especially in the spinal cord injury population. Id.

Accordingly, Chancellor underscores the unreliable and inconsistent success of treating ED in men having spinal cord injury. The combination of Beretta and Chancellor would lead one of ordinary skill in the art to have no reasonable expectation of success with either oral or transdermal application of therapeutic agents for treating ED in men with spinal cord injury.

Tay et al postulates that ED in men with spinal cord injury may be psychogenic in origin, compared to organic. Tay does not disclose methods of treating ED in men, having spinal cord injury, other than briefly noting the traditional methods of vacuum devices, intracavernous injection or penile prosthesis. Pg. 393.

Applicants' claimed invention requires that administration for the treatment of sexual dysfunction in an animal with an injured spinal cord be oral

and that the treatment employ a compound of formula (I). Applicants submit that one of ordinary skill in the art would not be motivated to combine Ellis with the secondary references: Beretta, Courtois, Chancellor and Tay. Applicants also submit that from the combination of teachings of the references, one of ordinary skill in the art would not have a reasonable expectation of success in treating ED in men having spinal cord injury. Likewise, Applicants submit that the references when combined do not teach or suggest all the claim limitations. Accordingly, Applicants respectfully request that the Examiner reconsider the rejection of the claims.

In particular, there is no suggestion to combine the references to arrive at Applicants' invention: (1) Ellis: oral administration of PDE5 compounds for the treatment of ED in men with no spinal cord injury. (2) Courtois: effectiveness of pharmacological treatments is dependent upon residual erectile capacity. And, the absence of pyschogenic and reflexogenic erections is consistent with organic aetiology; (3) Beretta: transdermal application of Minoxidil on men, having spinal cord injuries, resulted in approximate 25% success rate; (3) Chancellor: transdermal application of Minoxidil resulted in minimal, if any, erectile response in men having spinal cord injuries; and (4) Tay: ED in men having spinal cord injury may be psychogenic in origin, not organic.

Contrary to the Examiner's contention, one of ordinary skill in the art would not be motivated to use Applicants' vasoactive compounds for the treatment of ED in men with spinal cord injury. There is no teaching in the references or combined references to suggest that oral administration of PDE5 compounds is useful for treating ED in men, having spinal cord injury. Neither of the secondary references are directed to teaching oral administration of vasoactive compounds for the successful treatment of ED. In fact, Chancellor notes that oral administration of alpha-adrenergic antagonists had "limited" success, especially in the spinal cord injury population. Pg. 367, Col.2. Accordingly, Chancellor teaches away from oral administration. Furthermore, there is no teaching in any of the references that proper corpus cavernosum tissue in spinal cord injured men is a factor for sexual rehabilitation. To the contrary, Courtois teaches that rehabilitation is dependent upon residual erectile capacity – not proper cavernosum tissue -- which may be dependent upon the extent of damage to the pathways.

The Examiner further contends that one of ordinary skill in the art would be motivated to employ vasoactive compounds for the treatment of ED in men with spinal cord injury, since vasoactive compounds were known to be useful for treating ED in men with spinal cord injury. Applicant's respectfully disagree. One of ordinary skill in the art would not be motivated by the disclosures of the references cited herein. In fact, one of ordinary skill in the art would be discouraged from pursuing Applicants' invention, since transdermal application of Minoxidil had 0-25% success rate, depending upon which reference, Beretta or Chancellor, you rely on. Furthermore, the other disclosed successful methods of inducing an erection in men having spinal cord injury, such as intracavernous injection, would not motivate one of ordinary skill in the art to try oral adminstration of PDE5 inhibitor compounds.

Even if there were motivation to combine the references – which Applicants do not concede – there would be no reasonable expectation of success. For example, Beretta and Chancellor disagree as to the effectiveness of Minoxidil for treatment of ED in men, having spinal cord injury. Based upon the disclosed inconsistencies of the references one of ordinary skill in the art would not even have a reasonable expectation of success for treating ED in men having spinal cord injury, if the method of administration for a particular pharmacological treatment was transdermal application. In this instance, Applicants administration is oral and the reasonable expectation of success would even be lower. Furthermore, Courtois teaches that residual erectile capacity is an important factor in the successful treatment of ED in men having spinal cord injury. Accordingly, one of ordinary skill in the art would not reasonably expect successful treatment of ED in men having little or no residual erectile capacity.

Consequently, Applicants' claimed invention is not obvious from the claims of US 6, 469,012 or the disclosure of WO 94/28902 taken together with secondary references that disclose (1) different compounds (2) administered by different routes and (3) which may not even be effective. Because of the differences in compounds and in the route of administration, it is submitted one of ordinary skill would not combine US 6,469,012 or WO 94/28902 with either secondary reference in the first place. Because of the lack of an expectation of success (indeed, because of the negative results reported in Chancellor and

limited success reported in Beretta), one would not find the claimed invention obvious.

As discussed more fully in Applicants' prior response, the combination of references do not even rise to the level of making the invention "obvious to try." The law is emphatic that "obvious to try" is NOT the test of obviousness under 35 U.S.C. §103. American Hospital supply Corp. v. Travenol Laboratories, Inc., 223 USPQ 577, 582 (Fed. Cir. 1984).

In light of the above, Applicants respectfully request that the Examiner reconsider the rejection of Claims 1, 2 and 5-10.

CONCLUSION

Having addressed all points and concerns raised by the Examiner, Applicants respectfully submit that the application is in condition for allowance and request an early and favorable action in this application.

Respectfully submitted,

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